IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Kapin *et al.*

Serial Number: 09/929,381

Filed: August 13, 2001

Examiner: J. D. Goldberg

Group Art Unit: 1614

For: Method of Treating Angiogenesis-Related Disorders

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as First Class Mail in an envelope addressed to: Commissioner of Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on this date:

28 October 2003
Date

Barbara McKenzie
Name

Barbara McKenzie
Signature

DECLARATION UNDER 37 C.F.R. § 1.131

Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

We, MICHAEL A. KAPIN, PH.D., DAVID P. BINGAMAN, PH.D., D.V.M., DANIEL A. GAMACHE, PH.D., GUS GRAFF, PH.D. and JOHN M. YANNI, PH.D. hereby say and declare as follows:

1. We are co-inventors of the subject matter and claims that are currently pending in the above-identified patent application.

2. We understand that the Examiner in the referenced case has cited Yaacobi, U.S. Patent No. 6,416,777.

3. Prior to October 21, 1999, we conceived of the idea of using 3-benzoylphenylacetic acid derivatives to treat angiogenesis-related disorders. Attached as Exhibit A is a copy of slides from a presentation given to colleagues at our place of employment, and assignee of the present invention, Alcon Universal Ltd (now known as Alcon, Inc.), in a confidential presentation prior to October 21, 1999.

Exhibit A demonstrates reduction to practice of the use of a 3-benzoylphenylacetic acid derivative to treat angiogenesis-related disorders.

5. All dates deleted from Exhibit A are prior to October 21, 1999.

6. Yoseph Yaacobi is not an inventor of the present invention. Commonly owned U.S. Patent No. 6,416,777, is directed to ophthalmic drug delivery devices, of which Dr. Yaacobi is the inventor, for delivering a variety of drugs to the human eye. It is not directed to the use of benzoylphenylacetic acid derivatives to treat angiogenesis-related disorders.

7. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Respectfully submitted,

Date	MICHAEL A. KAPIN, PH.D.
10/28/03 Date	DAVID P. BINGAMAN, PH.D., D.V.M.
10-28-03 Date	DANIEL A. GAMACHE, PH.D.

10/28/03
Date

GUS GRAFF, PH.D.

Date

JOHN M. YANNI, PH.D.

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Exhibit A

Retina/Degenerative Disease Research
Therapeutic Targets

- Retinal Edema
- Posterior Segment Neovascularizaton
- Retinopathy - AMD
  - Acute
  - Chronic

Retina/Degenerative Disease Research

Personnel

Retinal Edema

M. Kapin

M. Lin

V. Shine

D. Gamache (1/4)

M. Brady

T. McDonough (1/2)

Neovascularizaton

D. Bingaman

K. Hudson

Retinopathy

R. Collier

E. Martin

R. Landers

P. Neill

Outside Payments: 425K

Retina/Degenerative Disease Research

Therapeutic Targets

- Retinal Edema
  - **Recommend compound to treat retinal edema**
- Neovascularization
  - **Establish in-house testing capability**
  - **Identify lead class as alternative to AL-3789**
- Retinopathy
  - **Identify alternative use of eliprodil**
  - **Establish capability to identify neuroprotective agents useful for treating age-related maculopathies and acute retinopathies**
  - **Complete LSB initial evaluation studies**

Retina/Degenerative Disease Research

Retinal Edema: Background

- **Major cause of visual dysfunction associated with:**
  - diabetic retinopathy
  - vein occlusion
  - surgical indications (post cataract CME, PRP)
  - Trauma
- **Novel Approach: no approved drugs**
- **Clinical Assessment: non-quantitative**

Assessment of Macular Edema

- **Contact lens fundus biomicroscopy**
  - subjective
  - significant normal interpatient variability complicates detection of early ME
- **Stereophotography**
  - objective record of retinal status at a point in time
- **Fluorescein angiography**
  - site of vascular leakage
- **Visual Acuity/Static Perimetry**
  - highly variable against subjective measure of ME

Current Treatment Of Macular Edema

- **Surgical:**
  - **Grid/focal laser photocoagulation**
    - **stabilization of visual acuity, rather than an improvement of visual acuity**
- **Pharmacological:**
  - **No drugs currently indicated for ME**
  - **Compounds under clinical evaluation**
    - **Carbonic Anhydrase Inhibitor (Dorzolamide) - Merck USA**
    - **PKC inhibitor (LY333531) - Lilly**
    - **NSAIDS - CME**

Imaging Retinal Thickness for Assessing Macular Edema

- ✓ **Heidelberg Retina Tomograph**
  - **(Heidelberg Instruments Inc.)**
  - **confocal scanning laser ophthalmoscope**
- **Ocular Coherence Tomography**
  - **(Humphrey)**
  - **Time delays from reflected optical signals**
- **Retinal Thickness Analyzer**
  - **(Ocumetrics)**
  - **scans successive slit images of the retina**

RETINAL EDEMA PROGRAM

Strategy

1. **Establish appropriate animal models of retinal edema/inflammation**
   - **mitogen mediated pan retinal edema**
   - **focal edema by argon laser photocoagulation**
2. **Develop and validate HRT technology to quantify retinal edema (thickness)**
3. **Assess efficacy of compounds and new leads**

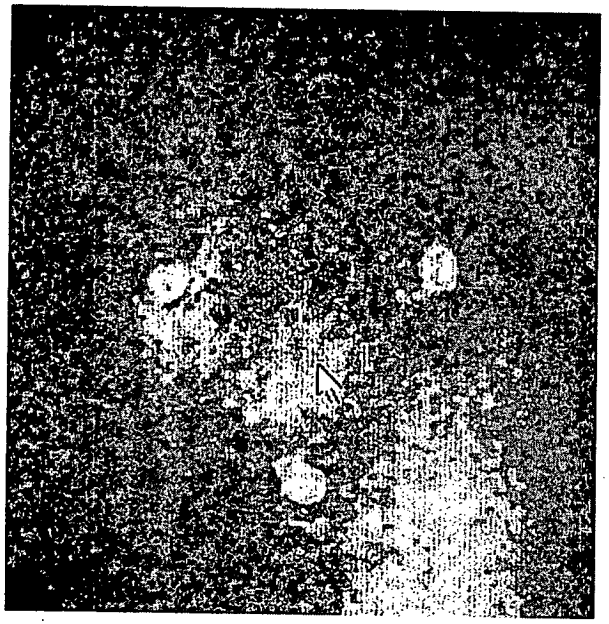
Mitogen Mediated Inflammation

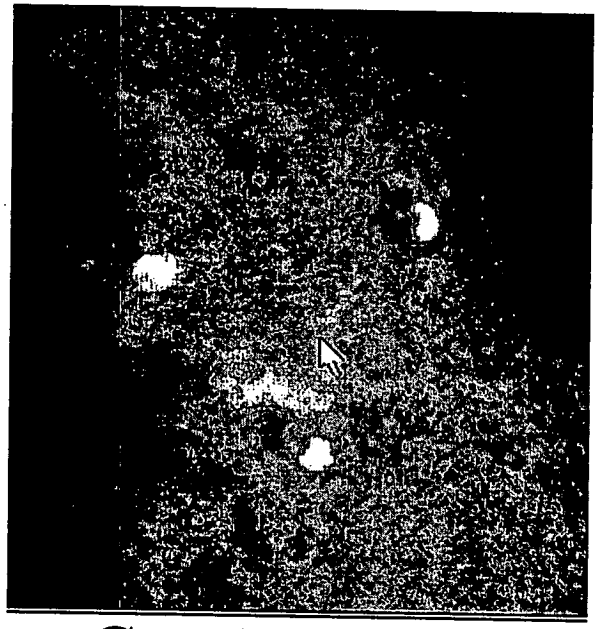
- **Intravitreal injection of Concanavalin A elicits in temporal sequence**
  - **expression of non-vascular low mw proteins in vitreous**
  - **vitreous TNFα**
  - **leukocyte influx into retina and choroid**
  - **blood-retinal barrier breakdown**
  - **increased NO in vitreous**
  - **decreased retinal docosahexaenoic acid**
  - **decreased retinal glutamic acid decarboxylase activity**
  - **decreased retinal choline acetyltransferase activity**
  - **deterioration of retinal architecture (SLO)**
  - **decreased ERG amplitude of A- and B-wave**

Retinal Thickness by Scanning Laser Ophthalmoscopy

- **HRT: confocal device for evaluating fundus topography (glaucoma)**
- **Retinal Thickness - New application**
  - **Collaborative effort by Heidelberg Instruments, U. Toronto (Dr. J. Flanagan) and Alcon Labs**
  - **Established "TView": automated software for measuring retinal thickness**
    - **→Retinal Thickness (Z profile) is a resulting plot of reflectance intensity versus scan depth**
    - **→Measures changes between vitreous/inner limiting membrane interface and the RPE**

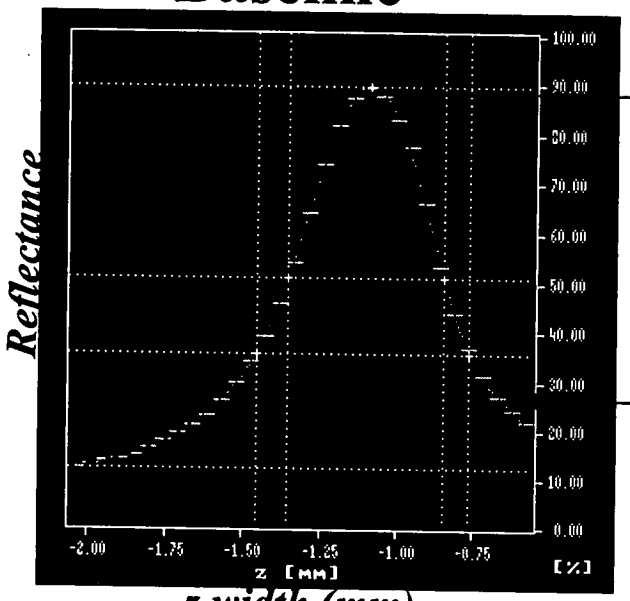
Thickness Derivation using the Heidleberg Retina Tomograph





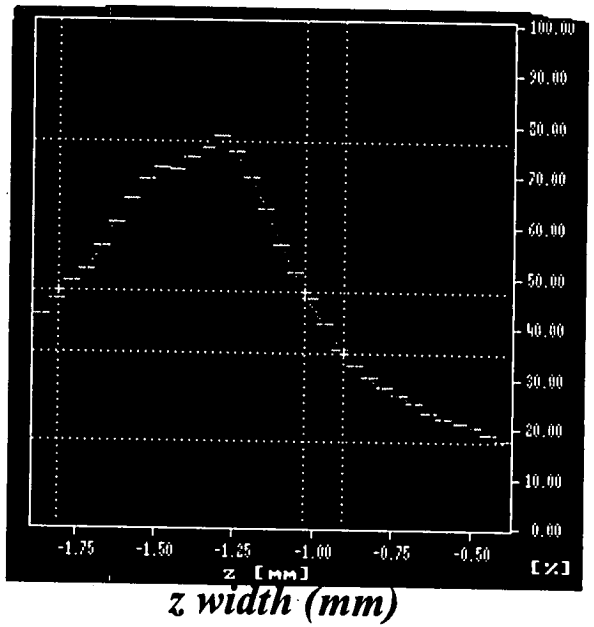
Baseline

Con A Treated



Vitreous / NFL Interface

RPE



Retinal Edema Program

Candidate Compounds

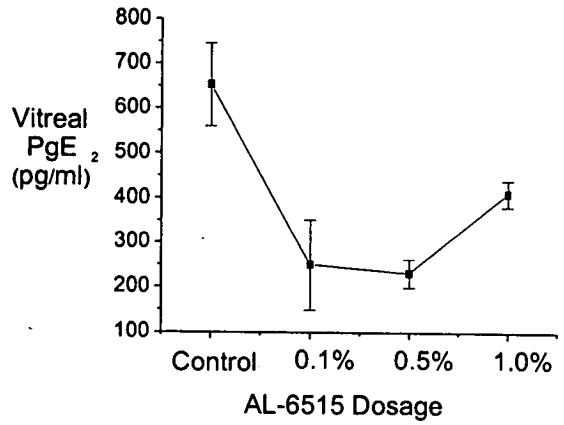
- AL-6515 (amfenac amide)
- AL-2512 (IOP safe steroid)
- AL-8417 (irrigating solution anti-inflammatory)
- AL-4862 (carbonic anhydrase inhibitor)

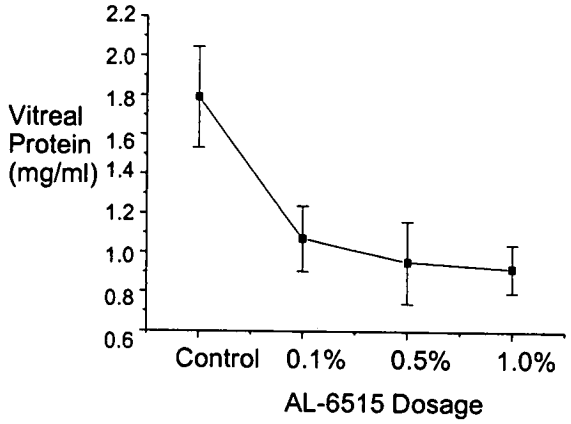
Retinal Edema Program

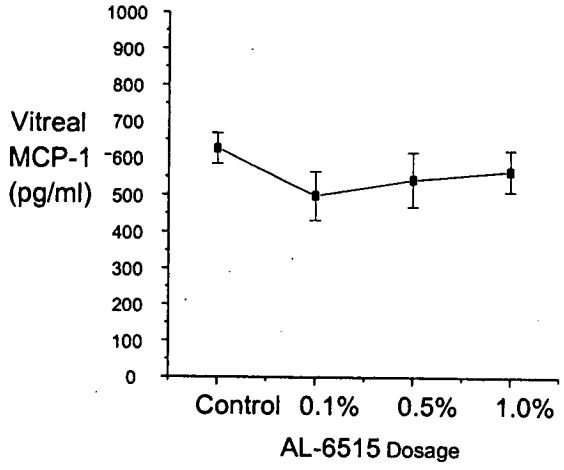
AL-6515 (Amfenac Amide)

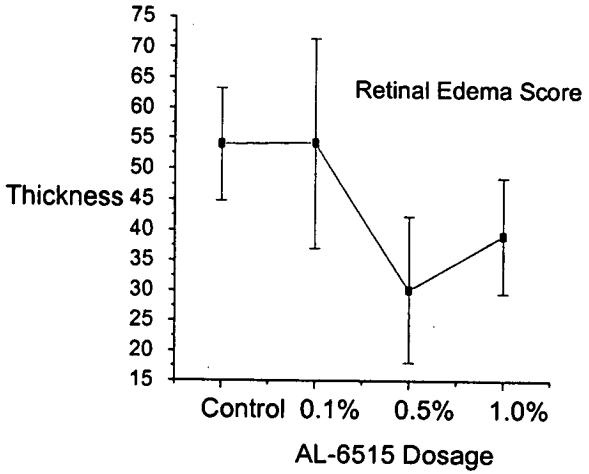
- Prostaglandin synthesis inhibitor
- Inhibits PG synthesis in posterior segment following topical dosing in rabbits
- Compound distributed to retina following topical administration to rabbits
- Clinical data indicates effect for pain, photophobia and inflammation

Effect of Topical AL-6515 on Markers of Inflammation and Retinal Thickness









Retinal Edema Program Status

- **AL-6515 Studies**
  - **dose-response studies - completed Q2**
  - **comparison with Voltaren (diclofenac 0.1%) and Acular (ketorolac 0.5%) - underway**
  - **evaluate contralateral effect in Con A administered eye:**
  - **recommend lead (PRB)**

Retina/Degenerative Disease Research Unit Plans

Retinal Edema Program

- **Identify lead anti-edema agent as backup to Nepafenac (AL-6515)**
  - **characterize anti-edema potential in Con A model of pan retinal edema. Assess activity by measuring changes in retinal thickness and biochemical markers of inflammation.**
- **Assess lead anti-edema agents of VEGF mediated vascular leakage.**
  - **Vascular leakage will be assessed with fluorescein angiography and quantified by fluorophotometry.**